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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/935,061	08/21/2001	Brian K. Kobilka	STAN-213	7757

24353 7590 08/26/2003
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EXAMINER

LI, RUIXIANG

ART UNIT PAPER NUMBER

1646

DATE MAILED: 08/26/2003

11

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

09/935,061

Applicant(s)

KOBILKA ET AL.

Examiner

Ruixiang Li

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 20 June 2003.
- 2a) ☐ This action is FINAL. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-19 is/are pending in the application.
- 4a) Of the above claim(s) 5-8 and 13-19 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-4 and 9-12 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 21 August 2001 is/are: a) ☐ accepted or b) ☒ objected to by the Examiner.
- Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.
- If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

- 13) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
- ☐ Certified copies of the priority documents have been received.
 - ☐ Certified copies of the priority documents have been received in Application No. _____.
 - ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.
- 14) ☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).
- a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

- | | |
|--|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) Paper No(s). _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO-1449) Paper No(s) <u>6 & 7</u> . | 6) <input type="checkbox"/> Other: |

DETAILED ACTION

Election/Restrictions

1. Applicants' election without traverse of Group I (claims 1-13), in Paper No. 10 is acknowledged. Applicants' election of species (i) in Paper No. 10 is also acknowledged. Claims 1-4 and 9-12 are readable upon the elected species.
2. Claims 1-19 are pending. Claims 1-4 and 9-12 are under consideration. Claims 5-8 and 13-19 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention or species, there being no allowable generic or linking claim. Election was made **without** traverse in Paper No. 10.

Priority

3. Acknowledgment is made of a claim for domestic priority under 35 U.S.C. 119(e) to a provisional application, 60/286,250, filed on August 21, 2001.

Drawings

4. The drawing filed on 08/21/2001 are objected by the Examiner because of handwritings on each drawing.

A proposed drawing correction or the corrected drawing is required in reply to the Office action to avoid abandonment of the application. The objection to the drawing will not be held in abeyance.

Information Disclosure Statement

5. The Information Disclosure Statements submitted on 6/5/2002 and 8/5/2002 have been considered by the Examiner.

Claim Rejections—35 USC § 112, 1st paragraph

6. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention; and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. Claims 1-4 and 9-12 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for identifying an agonist of a GPCR, β 2-adrenergic receptor (β 2AR), comprising detection of a decrease in the fluorescent intensity of FM bound to Cys265, does not reasonably provide enablement for a method for identifying an agonist of any other GPCRs comprising detecting a *change in a detectable signal*. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The factors that are considered when determining whether a disclosure satisfies enablement requirement include: (i) the quantity of experimentation necessary; (ii) the amount of direction or guidance presented; (iii) the existence of working examples; (iv) the nature of the invention; (v) the state of the prior art; (vi) the relative skill of those in the art; (vii) the predictability or unpredictability of the art; and

(viii) the breadth of the claims. *Ex Parte Forman*, 230 USPQ 546 (Bd Pat. App. & Int. 1986); *In re Wands*, 858 F. 2d 731, 8 USPQ 2d 1400 (Fed. Cir. 1988).

Claim 1 recites a method for identifying an agonist of a GPCR comprising detecting *a change in the detectable signal*. Claims 1-4 and 9-12 depend from claim 1. Thus, the claims, as written, encompass any GPCRs and any detectable labels attached to one or more amino acid residues within the third intracellular loop of the GPCR. However, the specification merely discloses that the interaction of β 2AR with an agonist results in a decrease in the detectable signal of the detectable label (See, e.g., Fig. 2, 4, and 6). On page 47 ([00169]), the specification specifically states that binding of the full agonist to FM- β 2AR induces a conformational change that leads to a decrease in fluorescence intensity of FM bound to Cys265. The specification further discloses that the reduction in fluorescence intensity of FM bound to Cys265 was reversed by an antagonist, e.g., ALP (See, e.g., legend to Fig. 2). Clearly, an agonist of β 2AR can be identified only by detecting a decrease in fluorescence intensity, but not *a change* in fluorescence intensity because the term "a change" literally means either an increase or a decrease. In addition, an antagonist also causes a change in the detectable signal, as shown in the specification (See, e.g., Fig. 2). Furthermore, the art teaches that antagonists induced a small but significant increase in base-line fluorescence (Gether et al, J.B.C 270:28268-28275, 1995; see abstract).

Finally, while the specification lists a number of GPCRs that may be used in the screening assays of the present invention (page 16) and asserts that a detectable label can be photochemical (e.g., fluorescent), biochemical or other means (bottom of

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page 4), only a fluorescent label has been used in identifying an agonist of β 2AR by detecting a decrease in the fluorescent intensity; no working examples or sufficient guidance are provided in the specification indicating or even suggesting that a signal from other detectable labels would be reduced when an agonist binds to a GPCR. There is no specific teaching in the art that signals from all detectable labels would be reduced when an agonist binds to a GPCR. It is unpredictable whether a signal from a specific detectable label attached to a GPCR would increase or decrease because there is no universal correlation between the conformational change of a GPCR and the intensity of a detectable label. Thus, it would require undue experimentation to confirm or determine whether a signal from a given detectable label decreases as does the fluorescent label.

Accordingly, the specification only enable for a method for identifying an agonist of β 2AR comprising detection of a decrease in the fluorescent intensity of FM bound to Cys265, but fails to enable for a method for identifying an agonist of any other GPCRs comprising detecting *a change in a detectable signal*.

Claim Rejections—35 USC § 112, 2nd paragraph

8. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

9. Claim 1-4 and 9-12 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 is indefinite because it recites "agonist activity in the preamble whereas the detecting step recites "agonist binding activity", causing confusion.

Claims 2-4 and 9-12 depend, either directly or indirectly, from claim 1.

Claim Rejections—35 USC § 102

10. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

11. Claims 1-4 and 9-12 are rejected under 35 U.S.C. 102 (b) as being anticipated by Gether et al. (IDS, The EMBO Journal 16:6737-6747, 1997).

Gether et al. teach a method for directly monitoring conformational changes in a G protein coupled receptor, beta2 adrenergic receptor induced by an agonist or an antagonist. The beta2 adrenergic receptor was covalently labeled by a cysteine-selective and environmentally sensitive, fluorescent probe, N,N'-dimethyl-N-(iodoacetyl0-N'-(7-nitrobenz-2-oxa-1,3-diazol-4-yl)ethylenediamine (IANBD). Gether et al. further teach attachment of IANBD to amino acid residues of the conformationally sensitive regions, including ²⁶⁵Cys in the third intracellular loop (See, e.g., Abstract; Figs. 1 and 2; and Table I). Since the measurement of fluorescence was done in a cuvette (see cited reference of Gether et al, J.B.C 270:28268-28275, 1995) containing 0.08% DβM (a detergent), the beta2 adrenergic receptor would be

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in a membrane of detergent micelles (see page 13 of specification for definition) and the beta2 adrenergic receptor would be attached to the cuvette, via either the N-terminal portion or C-terminal portion. Thus, the reference of Gether et al. meets the limitations of claims 1-4 and 9-12.

Claim Objections—Minor Informalities

12. Claim 1 is objected to because of an apparent typographic error in the claim, "having activity agonist activity" (line 1 of the claim). Appropriate correction is required.

Advisory Information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ruixiang Li whose telephone number is (703) 306-0282. The examiner can normally be reached on Monday-Friday, 8:30 am-5:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Yvonne Eyler, can be reached on (703) 308-6564. The fax phone number for this Group is (703) 305-3014 or (703) 308-4242.

Communications via Internet e-mail regarding this application, other than those under 35 U.S.C. 132 or which otherwise require a signature, may be used by the applicant and should be addressed to [yvonne.eyler@uspto.gov].


All Internet e-mail communications will be made of record in the application file. PTO employees do not engage in Internet communications where there exists a

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possibility that sensitive information could be identified or exchanged unless the record includes a properly signed express waiver of the confidentiality requirements of 35 U.S.C. 122. This is more clearly set forth in the Interim Internet Usage Policy published in the Official Gazette of the Patent and Trademark on February 25, 1997 at 1195 OG 89.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Ruixiang Li
Examiner
August 21, 2003


YVONNE EYLER, PH.D.
SUPERVISORY PATENT EXAMINER
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